PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL SEARCHING AUTHORITY

Translation

To:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43 *bis*.1)

Applicant's or agent's file reference PCT050629C	Date of mailing (*day/month/year*) 07 · JUL 2005 (07 · 07 · 2005) FOR FURTHER ACTION see paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/CN2005/000408	29.MAR.2005(29.03.2005)	01.APR.2004(01.04.2004)

International Patent Classification (IPC) or both national classification and IPC

IPC[7] C07K16/18 ,C12N15/13 ,15/63,15/70, A61K39/395,A61P35/00

Applicant

BEIJING ABT GENETIC ENGINEERING TECHNOLGY CO., LTD. et al.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No.II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i)with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No.VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No.VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/CN	Date of completion of this opinion	Authorized officer
The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	20.June.2005(20.06.2005)	WANG, Boli Telephone No. 86-10-62085225

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/CN2005/000408

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed
   ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material
      ☒ a sequence listing
      ☐ table(s) related to the sequence listing

   b. format of material
      ☐ on paper
      ☒ in electronic form

   c. time of filing/furnishing
      ☐ contained in the international application as filed
      ☒ filed together with the international application in electronic form
      ☐ furnished subsequently to this Authority for the purposes of search

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/CN2005/000408

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement:

Novelty (N)	Claims	4-13,15-20	YES
	Claims	1-3, 14	NO
Inventive step (IS)	Claims		YES
	Claims	1-20	NO
Industrial applicability (IA)	Claims	1-20	YES
	Claims		NO

2. Citations and explanations

D1: ACTA BIOCHIMICA et BIOPHYSICA SINICA, Vol.35,No.6
D2: HYBRIDOMA, Vol.9, No.1
D3: CN,A,1380341

2.1 Novelty:

Claims 1-3 and 14 lack novelty under PCT Article 33(2) as being anticipated by document 1(from page 503 to page 510). The document discloses a recombinant multifunctional single-chain trispecific antibody (scTsAb), which contains anti-ovarian carcinoma(OC) svFv, FC interlinker, anti-human CD3 scFv, HSA interlinker and V_H domain of anti-human CD28 antibody in turn. In addition, the scTsAb has a c-myc tag in the C termination. The antibody was constructed and expressed in *E.coli* BL21 Star strain. In order to harvest the recombinant protein, the culture was induced at 30℃ for 4h with 0.4 mmol/L IPTG. Moreover, the document 3(from page 7 to page 19 of the description) describes a cyclic single-chain trispecific antibody against human tumor which also comprises parts as described in the claims 1-3 of the present invention.

2.2 Inventive step:

Claims 4-13 and 15-20 lack an inventive step under PCT Article 33(3) as being obvious over document 1 in combination with document 2.

A mouse-human chimeric antibody specific for human carcinoebryonic antigen(CEA) was produced by recombinnant DNA techniques in the document 2(from page 43 to page 48). The nucleotide sequences and deduced amino sequences of the V_H gene and V_L gene of the anti-CEA antibody was also showed. So it would be obvious to one of the ordinary skilled in the art was made to obtain a scTsAb of claims 4-5 and 8-9 containing anti-CEA svFv, FC interlinker, anti-human CD3 scFv, HAS interlinker and V_H domain of anti-human CD28 antibody on the basis of document 1 and document 2. The techniques and methods for use are routinely determined in the gene engineering arts and do not bring out unexpected effect. The DNA sequences of the claimed scTsAb could be deduced according to triple codes. An expression vector containing the nucleotide sequences coding for the scTsAb and a host cell containing the expression vector were described in the document 1,whererin the vector was pTRI or psTRI and the host cell was *E.coli* BL21 Star. Thus, it would be obvious to one of the ordinary skilled in the art to get an expression vector as claimed in claim 10 or 11 and a host cell as claimed in claim 12 or 13 without the need for an inventive concept.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of Box V(Citations and explanations):

The additional features of dependent claims 15-16 could not confer inventiveness on which they depend because the feature of claim 15 was disclosed in the document 1 and the feature of claim 16 was a conventional method for purify protein in the art.

Document 1 also demonstrated that the scTsAb could be used for elimination of disseminated tumor cells. Certainly, it is easy for the skilled person to produce pharmaceutical combination with known antibodies. Consequently, the claims 17-20 of the present invention don't meet the requirements of PCT Article 33(3) in respect of inventive step.

2.3 Utility:

Claims 1-20 meet the criteria set out in PCT Article 33(4). The claimed invention would have been expected to have industrial applicability in the pharmaceutical field, e.g., in the treatment of cancer.

专 利 合 作 条 约

PCT

国际检索单位书面意见
(PCT 细则 43 之二 .1)

发信人：国际检索单位

收信人： 100101

中国北京市朝阳区慧忠路 5 号远大中心 B 座 18 层
隆天国际知识产权代理有限公司
王铮 刘锋

发文日 *(日/月/年)*
07 · 7月 2005 (07 · 07 · 2005)

申请人或代理人的档案号	后续行为
PCT050629C	见下面第 2 段

国际申请号	国际申请日 *(日/月/年)*	优先权日 *(日/月/年)*
PCT/CN2005/000408	29.3 月 2005(29.03.2005)	01.4 月 2004(01.04.2004)

国际专利分类(IPC)或国家分类和 IPC 两种分类
IPC[7] C07K16/18 ,C12N15/13 ,15/63,15/70, A61K39/395,A61P35/00

申请人
北京安波特基因工程技术有限公司 等

1.本意见包括关于下列各项的内容：

- ☒ I 意见的基础
- ☐ II 优先权
- ☐ III 不作出关于新颖性、创造性和工业实用性的意见
- ☐ IV 缺乏发明的单一性
- ☒ V 按照细则 43 之二.1(a)(i)关于新颖性、创造性或工业实用性的意见；支持这种意见的引证和解释
- ☐ VI 引用的某些文件
- ☐ VII 国际申请中的某些缺陷
- ☐ VIII 对国际申请的某些意见

2. 后续行为
如果提出初步审查要求书，本次意见将被视为国际初步审查单位(IPEA)的一次书面意见（如果申请人选择的国际初步审查单位非本单位，而且所选国际初步审查单位已按照细则 66.1 之二(b)通知国际局将不考虑国际检索单位的书面意见时例外）。
如本书面意见被视为国际初步审查单位的书面意见，则请申请人在自 PCT/ISA/220 发文之日起 3 个月或自优先权日起 22 个月内（以后届满者为准）向国际初步审查单位提交书面答复并提交修改（如适用），详情见 PCT/ISA/220 表格。

3. 详细信息请见 PCT/ISA/220 表格的说明

中华人民共和国国家知识产权局 (ISA/CN)	完成本意见的日期	受权官员
中国北京市海淀区蓟门桥西土城路 6 号 100088 传真号： (86-10)62019451	20.6 月 2005（20.06.2005）	汪波莉 电话号码：(86-10)62085225

PCT/ISA/237 表(扉页) (2005 年 4 月)

国际检索单位书面意见

国际申请号
PCT/CN2005/000408

I. 意见的基础

1、关于语言，制定书面意见基于：

☒ 申请提出时使用的语言。

☐ 该申请的_____语言译文，为了国际检索的目的提供该种语言的译文(细则 12.3(a)和 23.1(b))。

2、关于国际申请中所公开的核苷酸和/或氨基酸序列表和对所称发明的必要性，该书面意见是在下列基础上制定的：

a. 材料的类型

☒ 序列表

☐ 与序列表相关的表格

b. 材料的形式

☐ 纸件形式

☒ 电子形式

c. 提交/提供时间

☐ 包括于已提交的国际申请。

☒ 以电子形式与国际申请一起提交。

☐ 为检索之用随后提交本国际检索单位。

3、☐ 另外，在提交/提供了多个核苷酸和/或氨基酸序列表和/或与其相关的表格的版本或副本的情况下，提供了关于后提交的或附加的副本与已提交的国际申请中的序列表相同或未超出国际申请中序列表范围（如适用）的声明。

4. 补充意见

国际检索单位书面意见

国际申请号
PCT/CN2005/000408

V. 按细则 43 之二.1 关于新颖性、创造性或工业实用性的意见；支持这种意见的引证和解释

1. 意见

新颖性(N)	权利要求	4-13,15-20	是
	权利要求	1-3,14	否
创造性(IS)	权利要求		是
	权利要求	1-20	否
工业实用性(IA)	权利要求	1-20	是
	权利要求		否

2. 引证和解释

对比文件 1：生物化学与生物物理学报，第 35 卷第 6 期
对比文件 2：Hybridoma，第 9 卷第 1 期
对比文件 3：CN, A, 1380341

2.1 关于新颖性：

权利要求 1—3 和 14 相对于对比文件 1（第 503-510 页）不具有 PCT 第 33（2）条规定的新颖性。该对比文件公开了一种重组多功能单链三特异抗体（scTsAb），它由抗人卵巢癌单链抗体，FC 连接肽，抗人 CD3 单链抗体，HSA 连接肽和抗人 CD28 抗体 V_H 结构域片段依次连接而成。该 scTsAb 的 C 末端具有从 c-myc 标签。构建的抗体在大肠杆菌 BL21 中表达。为了收获重组蛋白，培养物用 0.4mmol/L 的 IPTG 在 30℃诱导表达 4 小时。此外，对比文件 3(说明书第 7-19 页)描述了一种抗人类肿瘤的环形单链三特异抗体，它也含有本发明权利要求 1-3 所述的抗体部分。

2.2 关于创造性：

权利要求 4—13 和 15—20 相对于对比文件 1 和对比文件 2 的结合不具有 PCT 第 33（3）条规定的创造性。

对比文件 2 中（第 43-48 页）利用 DNA 重组技术生产了一种抗人癌胚抗原（CEA）的鼠源嵌和抗体。同时公开了该抗 CEA 单抗重链可变区和轻链可变区的核苷酸序列和推导的氨基酸序列。这样，对本领域技术人员来说，在对比文件 1 和 2 的基础上得到权利要求 4—5 和 8—9 中含有抗 CEA 的单链抗体，FC 连接肽，抗人 CD3 单链抗体，HSA 连接肽和抗人 CD28 抗体 V_H 结构域片段的单链三特异抗体是显而易见的。所用的技术和方法是基因工程领域常用的，不会产生预料不到的效果。要求保护的 scTsAb 的 DNA 序列可由三联体密码推导获得。对比文件 1 还描述了含有 scTsAb 核苷酸序列的表达载体和含有表达载体的宿主细胞，其中载体是 pTRI 或 psTRI，宿主细胞是大肠杆菌 BL21。因此，对本领域技术人员来说，得到权利要求 10 或 11 要求保护的表达载体以及权利要求 12 或 13 要求保护的宿主细胞是显而易见的，不需要付出创造性劳动。

（见补充栏）

补充栏
(当前面的任何一栏篇幅不够时使用本栏)

续　　栏：接 V 栏第 2 部分

从属权利要求 15－16 的附加技术特征不能给它们引用的权利要求带来创造性，因为权利要求 15 的附加技术特征在对比文件 1 中已经公开，权利要求 16 的附加技术特征是本领域纯化蛋白的常规技术手段。

对比文件 1 还证明了 scTsAb 用于消除弥漫的肿瘤细胞。当然，本领域技术人员用已知抗体生产药物组合物是很容易的。因而，本发明权利要求 17－20 不符合 PCT 第 33（3）条关于创造性的规定。

2.3 关于实用性：

权利要求 1－20 符合 PCT 第 33（4）条关于实用性的规定。本发明在工业上可用于制备药物组和物，例如治疗癌症。